Clinical Policy: Fruquintinib (Fruzaqla)

Reference Number: CP.PHAR.666
Effective Date: 03.01.24
Last Review Date: 02.26
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Fruquintinib (Fruzaqla®) is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptor.

FDA Approved Indication(s)

Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-epidermal growth factor receptor (EGFR) therapy.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Fruzaqla is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all)**:**

1. Diagnosis of metastatic or advanced CRC (including appendiceal adenocarcinoma);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Documentation of RAS (KRAS or NRAS) wild-type gene status;
5. Member has progressed through all available regimens for CRC that include all the following agents,* unless clinically significant adverse effects are experienced or all are contraindicated (a-d):
   a. 5-fluorouracil or capecitabine;
   b. Oxaliplatin and irinotecan;
   c. An anti-VEGF agent (e.g., bevacizumab, Stivarga®, Zaltrap®, Cyramza®);
   d. If tumor expresses the RAS wild-type gene (i.e., mutation negative), an anti-EGFR agent: Erbitux® or Vectibix®;

   ** Prior authorization may be required*
6. Prescribed as a single agent;
7. For Fruzaqla requests, member must use fruquintinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Request meets one of the following (a or b):*
   a. Both of the following (i and ii):

i. Dose is at least 3 mg per day on days 1 to 21 of each 28-day cycle;
ii. Dose does not exceed 5 mg per day on days 1 to 21 of each 28-day cycle;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Colorectal Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Fruzaqla for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Prescribed as a single agent;
4. For Fruzaqla requests, member must use fruquintinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. Both of the following (i and ii):
      i. New dose is at least 3 mg per day on days 1 to 21 of each 28-day cycle;
      ii. New dose does not exceed 5 mg per day on days 1 to 21 of each 28-day cycle;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-FU: 5-fluorouracil
EGFR: epidermal growth factor receptor
CRC: colorectal cancer
FDA: Food and Drug Administration
KRAS: Kirsten rat sarcoma 2 viral oncogene homologue
NRAS: neuroblastoma RAS viral oncogene homologue
RAS: rat sarcoma
VEGF: vascular endothelial growth factor

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Fluoropyrimidine, oxalipatin, and irinotecan therapeutic agents and examples of regimens		
Example of fluoropyrimidine agents: • 5-FU (5-fluorouracil) • capecitabine (Xeloda®)	Varies upon protocol and patient tolerance	Varies
oxaliplatin	Varies upon protocol and patient tolerance	Varies
irinotecan (Camptosar®)	Varies upon protocol and patient tolerance	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of fluoropyrimidine-, platinum-, and/or irinotecan-containing regimens • FOLFOX = leucovorin/ 5-FU/oxaliplatin • CAPEOX = capecitabine/oxaliplatin • FOLFIRI = leucovorin/5-FU/irinotecan • FOLFOXIRI = leucovorin/5-FU/ oxaliplatin/irinotecan • IROX = irinotecan/oxaliplatin	Varies upon protocol and patient tolerance	Varies
Anti-VEGF agents		
bevacizumab (Avastin®, Alymsys®, Avzivi®, Jobevne™, Mvasi®, Vegzelma™, Zirabev™)	Varies	Varies
Zaltrap (ziv-aflibercept)	4 mg/kg IV every 2 weeks in combination with FOLFIRI	4 mg/kg every 2 weeks
Stivarga (regorafenib)	160 mg PO QD for the first 21 days of each 28-day cycle	160 mg/day
Cyramza (ramucirumab)	8 mg/kg IV every 2 weeks prior to FOLFIRI	8 mg/kg
Anti-EGFR agents		
Erbitux (cetuximab)	400 mg/m^2 IV for initial dose, then weekly infusions of 250 mg/m^2 IV OR 500 mg/m^2 IV every 2 weeks	See regimen
Vectibix (panitumumab)	6 mg/kg IV every 2 weeks	6 mg/kg every 2 weeks

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CRC	5 mg PO QD for the first 21 days of each 28-day cycle. Permanently discontinue Fruzaqla in patients unable to tolerate 3 mg PO QD	5 mg/day

VI. Product Availability

Capsules: 1 mg, 5 mg

VII. References

1. Fruzaqla Prescribing Information. Cambridge, MA. Takeda Pharmaceuticals America, Inc. February 2025. Available at: www.fruzaqlahcp.com. Accessed November 6, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 6, 2025.
3. National Comprehensive Cancer Network. Colon Cancer Version 5.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 6, 2025.
4. National Comprehensive Cancer Network. Rectal Cancer Version 4.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed November 6, 2025.
5. National Comprehensive Cancer Network. Appendiceal Neoplasms and Cancers Version 1.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/appendiceal.pdf. Accessed November 6, 2025.
6. Clinical Pharmacology [database online]. Tampa, FL: Elsevier; 2025. URL: www.clinicalkeys.com/pharmacology.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.11.23	02.24
1Q 2025 annual review: no significant changes; clarified RAS wild-type is mutation negative; references reviewed and updated.	10.24.24	02.25
1Q 2026 annual review: extended initial approval duration from 6 months to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.	11.06.25	02.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.